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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09/185,904	11/03/1998	CHRISTEN M. ANDERSON	660088.420	1190

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EXAMINER	
SCHNIZER, HOLLY G	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 01/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

FILE COPY

Office Action Summary	Application No. 09/185,904	Applicant(s) ANDERSON ET AL.	
	Examiner Holly Schnizer	Art Unit 1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)[X] Responsive to communication(s) filed on *16 October 2002* .

2a)[X] This action is **FINAL**. 2b)[ ] This action is non-final.

3)[ ] Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)[X] Claim(s) *1-42,44-52 and 56-101* is/are pending in the application.

4a) Of the above claim(s) *1-41 and 58-101* is/are withdrawn from consideration.

5)[ ] Claim(s) _____ is/are allowed.

6)[X] Claim(s) *42,44-52,56 and 57* is/are rejected.

7)[ ] Claim(s) _____ is/are objected to.

8)[ ] Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)[ ] The specification is objected to by the Examiner.

10)[X] The drawing(s) filed on *03 November 1998* is/are: a)[ ] accepted or b)[X] objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)[ ] The proposed drawing correction filed on _____ is: a)[ ] approved b)[ ] disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)[ ] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)[ ] Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)[ ] All b)[ ] Some * c)[ ] None of:

1.[ ] Certified copies of the priority documents have been received.

2.[ ] Certified copies of the priority documents have been received in Application No. _____ .

3.[ ] Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)[ ] Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) [ ] The translation of the foreign language provisional application has been received.

15)[ ] Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) [X] Notice of References Cited (PTO-892)
2) [ ] Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) [X] Information Disclosure Statement(s) (PTO-1449) Paper No(s) *16* .
4) [ ] Interview Summary (PTO-413) Paper No(s). _____ .
5) [ ] Notice of Informal Patent Application (PTO-152)
6) [ ] Other: .

DETAILED ACTION

Status of the Claims

The Amendment and Response filed October 16, 2002 (Paper No. 25 has been entered and considered. Claims 53-55 have been cancelled. Therefore, Claims 1-42, 44-52, and 56-101 are pending. Claims 1-41 and 58-101 have been withdrawn from consideration as being drawn to non-elected subject matter. Claims 42, 44-52, 56, and 57 have been considered in this Office Action.

Drawings

The drawings are objected to for reasons cited in the Form PTO 948 attached to Paper No. 8. Correction is required.

Objections/Rejections Withdrawn

The rejection of Claims 42 and 44-57under 35 U.S.C. 112, first paragraph, is withdrawn in light of the amendment of the claim to recite a specific ANT protein, ANT3 of SEQ ID NO:33.

The rejection of Claims 42 and 44-46 under 35 U.S.C. 102(a) as anticipated by Marzo et al. is withdrawn in light of the amendment of the claims to recite a protein with at least 95% identity to ANT3 of SEQ ID NO:33.

The rejection of Claims 42 and 44-46 under 35 U.S.C. 102(a) as anticipated by Fiore et al. is withdrawn in light of the amendment of the claims to recite a protein with at least 95% identity to ANT3 of SEQ ID NO:33.

The rejection of Claims 42 and 44-57 under 35 U.S.C. 103(a) as unpatentable over Fiore et al. in view of Rosenberg is withdrawn in light of the amendment of the claims to recite a protein with at least 95% identity to ANT3 of SEQ ID NO:33.

The rejection of Claims 42 and 44-57 under 35 U.S.C. 103(a) as unpatentable over Adrian et al. in view of Fiore et al. is withdrawn in light of the amendment of the claims to recite a protein with at least 95% identity to ANT3 of SEQ ID NO:33.

The rejection of Claims 42 and 46-57 under 35 U.S.C. 101 as claiming the same invention as that of claims 42, 46, 47, 48, 51, 52, 53, 56, and 57 of copending Application No. 09/393,441 is withdrawn in light of the amendment to the claims. At present, the claims of the present application encompass ANT3 polypeptides that do not localize to the mitochondrial membrane whereas the claims of the '441 patent are limited to those ANT3 polypeptides that localize to the mitochondrial membrane.

New Rejections Necessitated by Amendment

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 42, 46, 47, 48, 49, and 50 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 42, 46, 47, 48, 51, and 57 of copending Application No. 09/393,441. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claims because the examined claim is either anticipated by, or would have been obvious over, the reference claims. See e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 42, 46, 47, 48, 51, and 57 of the '441 application fall entirely within the scope of claims 42, 46, 47, 48, 49, and 50. Specifically, the ANT polypeptides comprising an amino acid sequence that is at least 95% identical to SEQ ID NO:33 and that localize to the mitochondrial membranes of Claims 42 and 46 of the '441 application are encompassed by the ANT polypeptides comprising an amino acid sequence that is at least 95% identical to the human ANT3 sequence of SEQ ID NO:33 of Claims 42 and 46 of the present application. In addition, the ANT fusion polypeptides comprising an amino acid sequence that is at least 95% identical to SEQ ID NO:33 and that localizes to the mitochondrial membranes and binds an ANT ligand of Claims 47 and 48 of the '441 application are encompassed by the ANT fusion polypeptides

comprising an amino acid sequence that is at least 95% identical to the human ANT3 sequence of SEQ ID NO:33 of Claims 47, 48, 49, and 50 of the present application. And, the ANT fusion polypeptides comprising an amino acid sequence that is at least 95% identical to SEQ ID NO:33 and that localizes to the mitochondrial membranes and binds an ANT ligand of Claims 51 and 57 of the '441 application are encompassed by the ANT fusion polypeptides comprising an amino acid sequence that is at least 95% identical to the human ANT3 sequence of SEQ ID NO:33 and that binds an ANT ligand of Claims 51 and 57 of the present application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 42, 45, 46, 52, and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cozens et al. (J. Mol. Biol. (1989) 261-280; ref. AL of IDS filed Sept. 6, 2000) in view of Le Saux (Biochemistry (1996) 35: 16116-16124).

Cozens et al. teach a human mitochrondrial ADP/ATP translocase protein, or ANT protein, that is 100% identical to the amino acid sequence of SEQ ID NO :33 (see attached sequence alignment). Since the protein taught by Cozens is an ANT protein, the protein would inherently bind an ANT ligand (regarding clm. 42). Moreover, it is an inherent property of an ANT protein that it would bind ATP, which competitively inhibits binding to atractyloside (regarding clm. 45). The examiner notes that the nomenclature used in Cozens for the ANT3 protein is T2.

Cozens et al. do not teach that the disclosed ANT3 protein was isolated.

Le Saux et al. teach the recombinant expression, isolation, and purification of Anc2p, the yeast homologue the human ANT3 described in Cozens et al. (see Le Saux et al., p. 16118, Col. 1, first two paragraphs and p. 16119, Col. 1, "Isolation of Anc2p"). The yeast cell used in ANT expression in Le Saux et al. is considered a lower eukaryotic cell that inherently lacks endogenous human ANT1 and human ANT2 polypeptides (regarding clms. 46 and 52). Le Saux et al. also teach that a variety of tryptophan mutated Anc2p proteins were expressed at the same level as the wild-type and that all expressed proteins had ligand binding activity (see abstract and p. 16120). The isolated ANT protein described by Le Saux et al. binds ATP; an ANT ligand that

competitively inhibits binding of atractyloside as evidenced By Roux et al. (p. 16120, paragraph spanning Col. 1-2; regarding clm. 45). Le Saux et al. show that the recombinant ANT polypeptide disclosed therein is expressed and is present in an intact mitochondrian (see p. 16120).

Therefore, with the combined teachings of Cozens et al. (providing the human ANT3 sequence) and Le Saux et al. (teaching successful expression of a related ANT protein in yeast cells) in hand, it would have been obvious to one of ordinary skill in the art at the time of the invention to express and purify the human ANT3 taught in Cozens et al. by using the method taught in Le Saux et al. ANT proteins have a central role in cellular energy metabolism and it is likely that dysfunction of these proteins is involved in mitochondrial disorders. Therefore, one of ordinary skill in the art at the time of the invention would have been motivated to substitute sequences having 95% homology to human ANT3 protein described in Cozens et al. in the method of Le Saux et al. in order to obtain sufficient amounts of the human ANT protein and its mutants for characterization. One of ordinary skill in the art at the time of the invention would have had a reasonable expectation of success in expressing and isolating the human ANT3 protein described in Cozens et al. since Le Saux et al. teaches successful expression and isolation of the related yeast homologue and several of its mutants. Thus, absent evidence that the human ANT3 protein could not be expressed in yeast, it appears that the claims are *prima facie* obvious over Cozens et al. and Le Saux et al.

Claims 42, 44-52, 56 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cozens et al. (J. Mol. Biol. (1989) 261-280; ref. AL of IDS filed Sept. 6, 2000) in view of Adrian et al. (Mol. Cell Biol. (1986) 6(2): 626-634; referenced Paper No. 8) and Rosenburg (Protein Analysis and Purification: Benchtop Techniques (1996) Birkhauser, Boston, pages 335-347; referenced in Paper No. 8).

Cozens et al. teach a human mitochrondrial ADP/ATP translocase protein, or ANT protein, that is 100% identical to the amino acid sequence of SEQ ID NO :33 (see attached sequence alignment). Since the protein taught by Cozens is an ANT protein, the protein would inherently bind an ANT ligand. The examiner notes that the nomenclature used in Cozens for the ANT3 protein is T2.

Cozens et al. do not teach that the disclosed ANT3 protein was isolated and do not teach an ANT fusion protein.

Adrian et al. disclose the expression of fusion proteins comprising *Saccharomyces cerevisiae* ADP/ATP translocator (ANT) proteins of various lengths (see p. 631, Fig. 5) and the enzyme β-Galactosidase (regarding clm. 48) in an investigation of what amino acids are important in targeting the protein to the mitochondrial membrane. β-Galactosidase has an affinity for ligands such as its substrates and antibodies (regarding clm. 57). The study reveals that several of the fusion proteins were delivered to the mitochondria (see p. 630, Col. 2, lines 23-30; and p. 631, Table 1; regarding clm. 49). Furthermore, it appears that the ANT polypeptides of Adrian et al. are capable of binding ANT ligands (see Fig. 6). The yeast host cell would not express endogenous human ANT1 or human ANT2 (regarding clm. 46).

Rosenburg teaches that it is standard in the art to construct fusion proteins between a protein of interest and an enzyme (for example β-galactosidase or β-Gal, see pages 336, lines 3-6 and the section titled "Expression and Purification of lacZ and trpE fusion proteins"). Rosenburg teaches that β-Gal can be used as a fusion partner to provide an advantage because antibodies to β-Gal can be used to affinity purify the fusion protein. This type of purification would separate the ANT protein from non-recombinant ANT proteins (regarding clm. 44). Rosenburg teaches that a protease cleavage site can easily be engineered into the fusion so that the fusion partner can be separated from the protein of interest after purification (see page 344, section 11.15).

Taken together, the above references teach a human ANT3 polypeptide sequence 100% identical to the sequence set forth in SEQ ID NO:33, a fusion protein of an ANT protein with the enzyme, β-Gal, in which β-Gal is capable of binding to lactose or an antibody and where the protein is engineered in a manner so that a protease may be used to separate the above fusion partners. It would have been obvious to a person of ordinary skill in the art at the time of the present invention to substitute the human ANT protein taught by Cozens et al. for the yeast ANT protein taught by Adrian et al. to obtain a fusion protein. It would have been obvious to a person of ordinary skill in the art at the time of the invention to engineer a protease cleavage site within the protein fusion construct as taught by Rosenburg. The skilled artisan would have been motivated to make the above modifications in order to facilitate the recombinant production and purification of the human ANT protein taught by Cozens et al. in order to study the mitochondrial localization sequence in the human ANT. Characterization of

human ANT proteins is essential to the development of diagnostic and treatment tools because these proteins have a central role in cellular energy metabolism and it is likely that dysfunction of these proteins is involved in mitochondrial disorders. One would have had a reasonable expectation of success in isolating human ANT polypeptides using the method of Adrien et al. since the preparation of a fusion protein with β-Gal and the incorporation of a protease cleavage site are standard methods in the art for recombinant production and rapid purification of proteins, and, in the case of Adrian et al., have been demonstrated with a highly homologous ANT protein. Thus, for the reasons stated above, it appears that the claims are *prima facie* obvious over the prior art.

Conclusion

In summary, the human ANT3 sequence, the methodology to express recombinant proteins and fusion proteins, and the successful expression of ANT proteins from other species were well known in the prior art at the time of the invention. Therefore, for the reasons stated above, it appears that the present claims are obvious over the prior art.

No Claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (703) 305-3722. The examiner can normally be reached Monday through Wednesday from 8 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703 308-0196.

HS

Holly Schnizer
January 8, 2003

CHRISTOPHER S. F. LOW
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